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Letter to the Editor

Vaginal and Cervical Cancers and Other Abnormalities Associated with Exposure *in Utero* to Diethylstilbestrol and Related Synthetic Hormones

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The National Cancer Institute is supporting a study of vaginal cancer and other noncancerous genital tract irregularities in offspring of mothers who received synthetic estrogens during pregnancy. The study, entitled The DESAD Project (DES[7] and Adenosis), seeks to provide answers concerning the risk to exposed offspring born after 1940 of developing cancer or other medically important conditions, including vaginal adenosis and cervical abnormalities. Each of 4 participating institutions[8] is identifying 500 or more subjects with documented *in utero* exposure. Exposed daughters of different ages are being examined and followed to determine incidence and natural history of vaginal adenosis and other irregularities.

Abnormalities Associated with Exposure *in Utero* to DES

DES, a synthetic estrogen-type hormone, was first synthesized in the late 1930's. During the 1940's many physicians in the United States and other countries prescribed this substance for pregnant women. Several studies suggested that in complications of pregnancy such as bleeding, threatened miscarriage, or diabetes, this treatment improved salvage of the fetus.

Later studies disclosed that the administration of DES during pregnancy was less effective than initially thought. Although its use in pregnancy has now been discontinued, DES remains a useful agent for certain menopausal symptoms, certain cases of carcinoma of the breast and prostate, and a few other clinical problems. A list of DES-type drugs is found in Table 1.

In 1971, Dr. Arthur L. Herbst, Dr. Howard Ulfelder, and Dr. David Poskanzer of Massachusetts General Hospital and the Harvard Medical School reported a link between maternal DES therapy during pregnancy and the later occurrence of clear-cell adenocarcinoma of the vagina in female offspring exposed to the drug *in utero*. This initial report was soon confirmed by others.

Soon after the discovery of the initial cases, a Registry of Clear-Cell Adenocarcinoma of the Genital Tract in Young Females was established by Dr. Herbst and Dr. Robert E. Scully with support from the National Cancer Institute and the American Cancer Society. It now contains varying amounts of data on almost 300 cases from the United States and abroad. The Registry address is MARP, Room 303, 5841 Maryland Avenue, Chicago, Ill. 60637.

The patients have ranged in age from 7 to 28 years at the time of diagnosis.

Documentation of exposure to DES-type hormones has been established in two-thirds of the fully investigated case histories. Of the vaginal adenocarcinoma cases, more than 80% are known to have been exposed to DES-type hormones. Because DES-type hormones were not administered to some of the mothers of these cancer patients, factors other than maternal hormone administration may also play a role in the etiology of these cancers.

In all cases for which precise treatment dates are available, the drug was initiated before the 18th week of gestation. Dosages and duration of therapy varied widely. However, as little as 1.5 mg DES administered daily throughout pregnancy was found in 1 case history to be associated with subsequent cancer in female offspring. Administration of the drug in varying amounts for a week or more during the 1st trimester also was associated with the subsequent development of cancer.

Cancers related to DES exposure have not been reported in male offspring.

Although the exact number of pregnant women treated with DES or chemically similar compounds during pregnancy is unknown, it has been estimated to be as many as 2

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[7] The abbreviation used is: DES, diethylstilbestrol.

[8] The institutions participating in this study, and the principal investigators, are: Massachusetts General Hospital, Harvard Medical School, Boston, Mass., Dr. Ann Barnes and Dr. Stanley J. Robboy; University of Southern California, Los Angeles, Calif., Dr. Duane E. Townsend; Baylor College of Medicine, Houston, Texas; Dr. Raymond H. Kaufman; and Mayo Clinic, Rochester, Minn., Dr. David G. Decker.

The Mayo Clinic is coordinating the efforts of the institutions participating in the study. Dr. Leonard T. Kurland, Chairman of the Department of Epidemiology and Medical Statistics at Mayo, is directing the study's National Coordinating Center. The Project Director at the National Cancer Institute, Division of Cancer Control and Rehabilitation, is Dr. Mary Ann Sestili, Room 6107, Blair Building, 8300 Colesville Road, Silver Spring, Md. 20910. The telephone number is (301)427-7477.

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Table 1

DES-type drugs that may have been prescribed to pregnant women

Nonsteroidal estrogens	
Benzestrol	Mikarol forti
Chlorotrianisene	Milestrol
Comestrol	Monomestrol
Cyren A	Neo-Oestranol I
Cyren B	Neo-Oestranol II
Delvinal	Nulabort
DES	Oestrogenine
DesPlex	Oestromenin
Diestryl	Oestromon
Dibestil	Orestol
Dienestrol	Pabestrol D.
Dienoestrol	Palestrol
Diethylstilbestrol dipalmitate	Restrol
Diethylstilbestrol diphosphate	Stil-Rol
Diethylstilbestrol dipropionate	Stilbal
Diethylstilbenediol	Stilbestrol
Digestil	Stilbestronate
Domestrol	Stilbetin
Estilben	Stilbinol
Estrobene	Stilboestroform
Estrobene DP.	Stilboestrol
Estrosyn	Stilboestrol DP.
Fonatol	Stilestrate
Gynben	Stilpalmitate
Gyneben	Stilphostrol
Hexestrol	Stilronate
Hexoestrol	Stilrone
Hi-Bestrol	Stils
Menocrin	Synestrin
Meprane	Synestrol
Mestilbol	Synthoestrin
Methallenestril	Tace
Microest	Vallestril
Mikarol	Willestrol
Nonsteroidal estrogen-androgen combinations	
Amperone	Teserene
Di-Erone	Tylandril
Estan	Tylosterone
Metystil	
Nonsteroidal estrogen-progesterone combination	
Progravidium	
Vaginal cream-suppositories with nonsteroidal estrogens	
AVC cream with Dienestrol	
Dienestrol cream	

million. The risk of developing adenocarcinoma in exposed females under 30 appears to be minimal, in view of the large exposed population and the very rare incidence of the disease so far reported. However, as exposed females grow older, the incidence of cancer related to DES-type drugs may change.

The cancers reported in the Registry have been found more often on the cervix or upper anterior vaginal wall than elsewhere. They usually are elevated, soft, and friable, with a tendency to invade surrounding tissue early and metastasize through the lymphatic system. The ratio of vaginal to cervical site of origin has been approximately 2:1.

Early in their investigation, Dr. Herbst and his associates noted that most of the vaginal and cervical cancers in the exposed females were associated with vaginal adenosis. Benign adenosis is found histologically in over 97% of vaginal clear-cell adenocarcinomas, whether or not a history of DES-type drug exposure *in utero* is confirmed. Vaginal adenosis is rare in normal (unexposed) young women.

The results of examinations of females exposed *in utero* to DES-type drugs have been reported in several studies. More than one-third of those who were exposed in the first 4 months of gestation have vaginal adenosis, and more than two-thirds have cervical ectropion. Other abnormalities seen in these examinations, such as transverse vaginal and cervical ridges, also may be associated with intrauterine exposure to DES-type drugs. These are described by a variety of names: hood, pseudopolyp, rim, collar, and cockscomb cervix.

Management of Females Exposed to DES-type Drugs

All asymptomatic girls who were exposed *in utero* should receive a thorough pelvic examination at menarche or if they have reached 14 years of age. Younger girls should be examined if they develop abnormal bleeding or discharge. Whenever prenatal exposure is probable and there are symptoms of discharge, further investigation is imperative, regardless of the patient's age. This investigation should not be concluded until it is certain that no lesion is present.

Before the examination is undertaken, the entire procedure should be thoroughly discussed with the patient (and her mother or father if she is a minor).

The examination should include inspection and palpation, Papanicolaou smear (cervix and vagina), and an iodine staining test of the entire cervix and vagina. Abnormal areas, including those that do not stain with iodine, should be biopsied. This procedure can be performed in the physician's office with small biopsy instruments and without significant discomfort.

For the very young patient who has symptoms that require investigation, anesthesia may occasionally be required before an examination. A small speculum permits adequate visualization of the vagina without undue discomfort in younger patients.

With asymptomatic females, if adequate examination is not possible at the initial visit, vaginal tampons should be used for a few months to allow an adequate examination later without discomfort. Colposcopy is a useful adjunct to this examination, but it is not essential. Utilizing its low-power magnification to examine the vagina and cervix, the physician can identify areas of glandular tissue (adenosis) in the vagina or on the cervix. This identification permits directed rather than "blind" biopsies. When used in conjunction with the iodine staining test and selected biopsy, colposcopy permits precise recording of observed abnormalities and their appraisal at fixed intervals.

The patient exposed to DES-type drugs should be followed on a regular basis. After a normal initial examination, annual pelvic examinations with cervical and vaginal cytology and iodine staining are probably adequate. If any abnormalities are noted during the initial evaluation, more frequent follow-up examinations are suggested (every 3 to 6 months, depending on the severity of the findings).

Locally destructive measures such as cauterization, cryosurgery, or excision can be utilized if atypical changes such as marked squamous dysplasia or carcinoma *in situ* of

the vagina or cervix are found on biopsy.

Optimal management of nonmalignant lesions in females exposed to DES-type drugs *in utero* is uncertain. At the present time, no case has been reported in which vaginal adenosis has progressed to cancer under direct observation. Careful follow-up appears at present to be the most prudent approach to DES-exposed subjects without carcinoma.

To date, there is no evidence indicating that use of oral contraceptives by the DES-exposed population would be undesirable. However, they do add additional hormonal variables to a complex situation and are one more aspect of the problem that requires further information.

The presence of adenosis is not a contraindication to future pregnancy, in case the woman desires to have children.

Decisions regarding mode and extent of therapy in these young women are difficult in themselves and are further complicated by emotionally charged issues. Both surgery and high-energy radiotherapy can potentially cure the disease. Cancers associated with DES-type drugs may develop in young women primarily in tissues of Müllerian orgin: the upper portion of the vagina and the cervix.

Treatment should be highly individualized and is best accomplished by physicians experienced in treating gynecological cancers.

A useful bibliography on the subject of DES exposure *in utero* follows. Readers desiring further information may obtain without charge 3 publications from the Office of Cancer Communications, National Cancer Institute, by using the card enclosed in this issue of CANCER RESEARCH.

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